

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1 1 (currently amended): A method of screening for the integration of a DNA
2 construct into a target gene having expression in the same cell or tissue type as a promoter
3 having restricted expression in a mouse, said method comprising:
4 (i) transforming a mouse ES cell with a first DNA construct encoding a first
5 indicator component under the control of ~~[[a]]~~ said promoter ~~having restricted expression in a~~
6 ~~mouse~~;
7 (ii) transforming the cell of (i) or a descendent of the cell by operably
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a second
9 indicator component not operably linked to a transcription control element;
10 (iii) producing tissue or specialized cells from the cell of (ii); and
11 (iv) monitoring the tissue or specialized cells of (iii) for a detectable indicator
12 resulting from both the first and second indicator components indicative of integration of the
13 second DNA construct into ~~[[a]]~~ said target gene ~~having restricted expression~~.

2 (canceled)

1 3 (currently amended): The method of ~~claims~~ claim 1 wherein the first and
2 second indicator components are inactive fragments or subunits of an enzyme which, when
3 combined, provide an active enzyme detectable by its activity.

1 4 (previously presented): The method of claim 1 wherein the first and second
2 indicator components are independently detectable or selectable, and the detectable indicator is
3 the presence of both indicator components in a cell.

1 **5** (previously presented): The method of claim **1** wherein the first and second
2 indicator components react in a sequence of reactions which result in a detectable indicator.

1 **6** (currently amended): The method of claim **1** which additionally comprises
2 isolating DNA endogenous to the mouse ES cell or descendent thereof which flanks the second
3 DNA construct integrated into [[a]] said target gene ~~having restricted expression~~.

7-8 (canceled)

1 **9** (previously presented): A DNA construct comprising, in a 5' to 3' direction, a
2 splice acceptor, a sequence encoding an inactive subunit or fragment of an enzyme and, an IRES
3 wherein said sequence encoding the enzyme subunit or fragment is not operably linked to a
4 transcription control element, and wherein said subunit or fragment is active when combined
5 with a further subunit.

10-11 (canceled)

1 **12** (previously presented): The combination of:

2 (i) a DNA construct for integration into the genome of an eukaryotic cell
3 comprising a sequence encoding a first indicator component under the control of a promoter
4 having restricted expression; and

5 (ii) a DNA construct for integration into the genome of a eukaryotic cell,
6 comprising in the 5' to 3' direction, a splice acceptor, a sequence encoding a second indicator
7 component not operably linked to a transcription control element, and an optional IRES, wherein
8 expression of both the first and second indicator components in said cell is detectable, and
9 wherein if said first indicator component is an antibiotic resistance marker, said second indicator
10 component is not an antibiotic resistance marker.

1 **13** (previously presented): A mouse ES cell or descendent thereof, transformed
2 by the combination of DNA constructs of claim **12**.

14 (canceled)

1 15 (previously presented): A DNA construct comprising, in a 5' to 3' direction, a
2 splice acceptor and a sequence encoding an inactive alpha or omega fragment of β -galactosidase,
3 wherein said sequence encoding the inactive alpha or omega fragment is not operably linked to a
4 transcription control element and said fragment is active when combined with another fragment
5 of β -galactosidase.

1 16 (currently amended): A method of screening for the integration of a DNA
2 construct into a target gene having expression in the same cell or tissue type as a promoter
3 having restricted expression in a mouse, said method comprising:

4 (i) transforming a mouse ES cell with a first DNA construct encoding a first
5 indicator component linked to ~~[[a]] said promoter having restricted expression in a mouse,~~
6 wherein DNA encoding the first indicator component is separated from said promoter by a
7 sequence of DNA which prevents transcriptional control by said promoter over the DNA
8 encoding the first indicator component;

9 (ii) transforming the cell of (i) or a descendent of the cell by operably integrating
10 into the cell's genome, a second DNA construct comprising DNA encoding a second indicator
11 component not operably linked to a transcription control element;

12 (iii) producing tissue or specialized cells of (ii); and

13 (iv) monitoring the tissue or specialized cells of (iii) for a detectable indicator
14 resulting from both the first and second indicator components indicative of integration of the
15 second DNA construct into ~~[[a]] said target gene having restricted expression,~~ wherein in the
16 second DNA construct, the second indicator component is a recombinase capable of removing
17 the sequence of DNA preventing transcriptional control in the first DNA construct; and,

18 wherein said monitoring is for cells in which the first indicator component is
19 expressed under the transcriptional control of the promoter having restricted expression.

1 17 (previously presented): The method of claim 16 wherein the DNA preventing
2 transcriptional control is flanked by lox sites and the recombinase is Cre.

1 18 (currently amended): A method of producing mouse tissue or specialized
2 cells comprising a detectable indicator associated with a target gene having expression in the
3 same cell or tissue type as a promoter having restricted expression in a mouse, which comprises:

4 (i) transforming a mouse ES cell with a first DNA construct encoding a first
5 indicator component under the control of ~~[[a]] said promoter having restricted expression in a~~
6 ~~mouse~~;

7 (ii) transforming the cell of (i) or a descendent of the cell by integrating into
8 the cell's genome, a second DNA construct comprising DNA encoding a second indicator
9 component not operably linked to a transcription control element;

10 (iii) producing tissue or specialized cells from the cell of (ii); and

11 (iv) selecting tissue or specialized cells of (iii) by the presence of a detectable
12 indicator resulting from both the first and second indicator components.

1 19 (currently amended): A method of producing a mouse comprising a
2 detectable indicator associated with a target gene having expression in the same cell or tissue
3 type as a promoter having restricted expression in a mouse, which comprises:

4 (i) transforming a mouse ES cell by integrating into the cell's genome, a first
5 DNA construct encoding a first indicator component under the control of ~~[[a]] said promoter~~
6 ~~having restricted expression~~;

7 (ii) transforming the cell of (i) or a descendent of the cell by integrating into
8 the cell's genome, a second DNA construct comprising DNA encoding a second indicator
9 component not operably linked to a transcription control element;

10 (iii) selecting transformed cells of (ii);

11 (iv) introducing selected cells of (iii) into a mouse host embryo;

12 (v) implanting the host embryo of (iv) into a pseudopregnant mouse;

- 13 (vi) maintaining the mouse of (v) while offspring develops to term from the
14 host embryo; and
15 (vii) selecting offspring of (vi) by the presence of a detectable indicator
16 resulting from both the first and second indicator components in tissue or specialized cells of the
17 offspring.